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Prevalence of Extended-Spectrum β-Lactamase-Producing *Enterobacter cloacae* in the Asia-Pacific Region: Results from the SENTRY Antimicrobial Surveillance Program, 1998 to 2001

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Enterobacter cloacae **strains from hospitalized patients with a range of infections were collected by 17 laboratories in the Asia-Pacific region and South Africa. Isolates for which ceftriaxone MICs were above 1 μg/ml and/or ceftazidime MICs were above 2 μg/ml, as well as 46 strains for which ceftriaxone and/or ceftazidime MICs were at or below these values, were screened for levels of extended-spectrum β-lactamase (ESBL) production through the use of broth microdilution for the detection of clavulanate enhancement of the activity of ceftriaxone, ceftazidime, and cefepime. Of the isolates examined, ceftriaxone and/or ceftazidime had elevated MICs for 44%, of which 36% were ESBL positive. ESBL-positive strains were commonly susceptible to piperacillin-tazobactam and more frequently resistant to several other antimicrobials studied. A cefepime MIC above 0.25 μg/ml had the highest sensitivity (100%) and specificity (74%) for predicting the presence of an ESBL.**

Enterobacter cloacae is commonly encountered as a nosocomial pathogen (27) and is therefore under intensive selective pressure from broad-spectrum β-lactam usage. It is the most commonly isolated member of the *Enterobacteriaceae* that possess chromosomal group-1 β-lactamases. The emergence of resistance to broad-spectrum cephalosporins in *E. cloacae* is well recognized as a consequence of the selection of mutants stably derepressed for the production of a group 1 β-lactamase (18, 27).

In recent years, it has also become apparent that this species can acquire and express genes encoding extended-spectrum β-lactamases (ESBLs) (6, 24). While common in *Klebsiella pneumoniae* and (to a lesser extent) *Escherichia coli*, these ESBL genes are known to spread to other members of the *Enterobacteriaceae*, but to date this appears to occur infrequently (4, 14, 24).

The presence of ESBLs in *Enterobacteriaceae* (*E. coli* or *Klebsiella* spp.) is generally suspected when broad-spectrum cephalosporin MICs are raised compared to those seen for normal strains and when the activity of broad-spectrum cephalosporins is significantly improved in the presence of clavulanate. However, elevated MICs of broad-spectrum cephalosporins for *Enterobacter* species usually imply stable derepression of the Bush group 1 enzyme (5). The Bush group 1 enzymes are generally not inhibited by the presence of clavulanate. Hence, enhanced broad-spectrum cephalosporin activity with *Enterobacter* species is highly suggestive of the presence of an ESBL.

This work was presented in part at the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada, 17 to 20 September, 2000 (paper 1988).

Clinically significant strains of bacteria from the SENTRY program were collected in 17 hospitals (in 8 countries or locales) in the Asia-Pacific region and South Africa between 1998 and 2001. The isolates were from hospitalized patients with bacteremia or lower respiratory infections, wound or soft-tissue infections, or urinary infections and from a range of intensive-care patient infection sites.

All isolates were initially tested by broth microdilution (according to National Committee for Clinical Laboratory Standards [NCCLS] methods) (21) with 30 compounds, including ceftazidime, ceftriaxone, cefepime, ticarcillin-clavulanate, piperacillin-tazobactam, ciprofloxacin, gentamicin, and imipenem. The breakpoints for resistance were those recommended by the NCCLS (22).

All isolates for which ceftriaxone MICs were >1 μg/ml and/or ceftazidime MICs were >2 μg/ml (the screening concentrations) were selected for confirmatory testing. A concentration of >2 μg/ml was chosen for ceftazidime (instead of the >1 μg/ml concentration recommended by the NCCLS) because the lowest concentration tested in 2001 was 2 μg/ml. However, of the 200 strains collected from 1998 to 2001 that did not undergo ESBL phenotypic testing, ceftazidime had a MIC of 2 μg/ml for none, confirming that a cutoff of >2 μg/ml was reasonable for this compound. A total of 46 strains for which ceftriaxone MICs were ≤1 μg/ml and ceftazidime MICs were ≤2 μg/ml were also examined (by determinations of false-negative values) to verify that the confirmatory test was valid.

ESBL phenotype testing was conducted as recommended by the NCCLS in Table 2a of document M7-A5 (21). Phenotypic confirmatory tests were performed with an agar dilution method using ceftriaxone, ceftazidime, and cefepime with and without 4 μg of clavulanate/ml. A reduction in MIC of ≥3 $\log_2$

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TABLE 1. Prevalence of reduced third-generation cephalosporin susceptibility and ESBL production among *Enterobacter cloacae* strains accessed by country and year

Country or locale	1998			1999			2000			2001			4-yr totals		
	No. of strains	% CRO or CAZ R[a]	% ESBL positive	No. of strains	% CRO or CAZ R[a]	% ESBL positive	No. of strains	% CRO or CAZ R[a]	% ESBL positive	No. of strains	% CRO or CAZ R[a]	% ESBL positive	No. of strains	% CRO or CAZ R[a]	% ESBL positive
Australia	33	45	6	45	36	2	55	36	2	45	31	7	178	37	4
Hong Kong	8	75	25	9	22	0	10	40	0	9	44	0	36	44	6
Japan	22	9	5	32	47	0	33	36	6	14	43	0	101	35	3
Mainland China	25	48	28	13	92	54	0			0			38	61	37
Philippines	19	58	37	27	56	33	37	57	43	11	45	9	94	55	35
Singapore	14	48	29	2	0	0	9	89	89	2	0	0	27	52	44
South Africa	7	29	14	6	67	0	18	39	33	23	48	17	54	44	20
Taiwan	8	63	38	2	50	0	10	30	0	39	56	21	59	53	19
Total	136	43	20	136	47	13	172	44	19	143	43	11	587	44	16

[a] Percentages of strains for which a ceftriaxone (CRO) MIC of >1 μg/ml and/or a ceftazidime (CAZ) MIC of >2 μg/ml was detected. R, resistant.

dilutions in the presence of clavulanate for one or more of the three cephalosporins was interpreted as evidence of ESBL production.

Between April 1998 and December 2001, 587 isolates of *E. cloacae* (accounting for 2.8% of all isolates received) were referred. By conventional NCCLS breakpoint criteria, 15% of the strains were intermediate and 21% were resistant to ceftriaxone. The strains were 4% intermediate and 35% resistant to ceftazidime and 1% intermediate and 3% resistant to cefepime.

Application of the ESBL screening MIC criteria selected 260 (44%) strains; the MICs of both ceftriaxone and ceftazidime were elevated for 247 of the strains, the MIC of ceftriaxone alone was elevated for 9 of the strains, and the MIC of ceftazidime alone was elevated for 4 of the strains. Rates of screening positivity differed between countries and by year for each country, with the 4-year average ranging from 35% in Japan to 61% in mainland China (Table 1).

Presumptive ESBLs were detected in 93 (35.8%) of the 260 ceftazidime and/or ceftriaxone screen-positive strains (or 15.8% of all *E. cloacae* isolates). None of the 46 screen-negative strains returned positive results in the phenotypic confirmatory test (100% specificity). Where there were sufficient numbers of isolates, considerable variation (range, 0 to 89%) in the rates of ESBL positivity from year to year and between countries was seen (Table 1). Average rates across all 4 years ranged from 3% in Japan to 44% in Singapore. In three countries, mainland China, the Philippines, and Singapore, rates exceeded 35%. As a proportion of all screen-positive strains, the proportion of ESBL-positive strains over the 4 years ranged from 9% in Japan to 86% in mainland China (data not shown).

Strains with the ESBL phenotype were much more likely to be nonsusceptible to multiple other antimicrobials than either ceftazidime-ceftriaxone-susceptible or -resistant strains without presumptive ESBLs (Table 2). Indeed, resistance to piperacillin-tazobactam, cefepime, ciprofloxacin, gentamicin, or trimethoprim-sulfamethoxazole was uncommon among ceftazidime-ceftriaxone-susceptible isolates and only 11% were not susceptible to ticarcillin-clavulanate. Of the 241 strains for which ceftazidime and/or ceftriaxone MICs were >8 μg/ml, only 3% were intermediate to cefepime and 7% were resistant.

TABLE 2. Prevalence of resistance to other antimicrobials in *Enterobacter cloacae* by β-lactamase phenotype

Strain characteristics and country or locale	No. of strains	Percentage of strains not susceptible to[a]:					
		TIM	TZP	FEP	CIP	GEN	SXT
Ceftriaxone and ceftazidime susceptible (MICs of ≤1 and ≤2, respectively)							
Australia	113	6	0	0	1	0	3
Hong Kong	19	30	0	0	0	0	5
Japan	64	11	0	0	2	0	2
Mainland China	14	13	0	0	7	0	7
Philippines	42	12	0	0	5	0	10
Singapore	13	8	0	0	0	0	8
South Africa	30	17	0	0	0	0	3
Taiwan	28	14	0	0	4	4	14
Total	323	11	0	0	2	<1	5
Ceftriaxone MIC of >1 and ceftazidime MIC of >2							
ESBL negative							
Australia	58	95	76	0	3	3	10
Hong Kong	14	100	79	7	29	14	29
Japan	32	100	81	9	28	25	28
Mainland China	9	100	89	0	67	67	44
Philippines	19	95	79	5	53	42	53
Singapore	2	100	50	0	0	0	50
South Africa	13	100	92	15	15	23	23
Taiwan	20	80	60	5	20	40	40
Total	167	95	77	5	22	22	27
ESBL positive							
Australia	7	100	29	0	0	100	86
Hong Kong	2	100	100	0	100	100	100
Japan	3	100	33	67	33	0	33
Mainland China	14	100	57	64	79	86	71
Philippines	33	91	24	0	33	48	91
Singapore	12	92	25	25	50	58	83
South Africa	11	82	18	9	18	91	91
Taiwan	11	91	36	18	18	91	91
Total	93	92	32	18	38	69	85

[a] Abbreviations: TIM, ticarcillin-clavulanate; TZP, piperacillin-tazobactam; FEP, cefepime; CIP, ciprofloxacin; GEN, gentamicin; SXT, trimethoprim-sulfamethoxazole.

TABLE 3. MIC and susceptibility patterns predictive of ESBL production

Strain and susceptibility pattern	No. of strains that were:		Sensitivity (%)	Specificity (%)	Positive predictive value (%)
	ESBL positive	ESBL negative			
All strains	93	494			
Cefepime MIC, >0.25 μg/ml	93	129	100	74	42
Aztreonam MIC, >1 μg/ml	93	159	100	68	37
Ceftazidime MIC, >2 μg/ml	92	166	99	68	37
Ceftriaxone MIC, >1 μg/ml	93	163	100	67	36
Piperacillin-tazobactam MIC, ≤16 μg/ml	63	365	68	26	15
Nalidixic acid MIC, >8 μg/ml	69	84	74	83	45
Ciprofloxacin MIC, >1 μg/ml	35	43	38	91	45
Tetracycline MIC, >8 μg/ml	63	55	68	92	62
Gentamicin MIC, >4 μg/ml	64	41	69	92	63
Trimethoprim-sulfamethoxazole MIC, >1 μg/ml	79	47	69	88	56
Subset of strains for which ceftazidime MICs were >2 μg/ml or ceftriaxone MICs were >1 μg/ml	93	167			
Cefepime MIC, >0.25 μg/ml	93	124	100	26	43
Piperacillin-tazobactam MIC, ≤16 to 4 μg/ml	61	38	68	77	62
Nalidixic acid MIC, >8 μg/ml	69	63	74	62	52
Ciprofloxacin MIC, >1 μg/ml	35	37	38	78	49
Gentamicin MIC, >4 μg/ml	64	37	69	78	63
Tetracycline MIC, >8 μg/ml	63	55	68	78	64
Trimethoprim-sulfamethoxazole MIC, >1 μg/ml	79	45	85	73	64

Of those strains with the ESBL phenotype, 3% were cefepime intermediate and 15% were resistant. One notable feature of the ESBL phenotype was the lower rate of nonsusceptibility to piperacillin-tazobactam (32%) compared to that of the non-ceftazidime-ceftriaxone-susceptible ESBL-negative strains (77%). Almost all strains of all phenotypes were susceptible to imipenem; the imipenem MIC for one non-ceftazidime-ceftriaxone-susceptible ESBL-negative strain was intermediate (8 μg/ml).

Susceptibility profiles of non-ceftazidime-ceftriaxone-susceptible strains were examined to determine whether any pattern might distinguish the ESBL-negative (stably derepressed only) phenotype from the ESBL-positive phenotype. ESBL-positive strains were more likely than ESBL-negative strains (18% versus 5%; $P < 0.001$) to require cefepime MICs above 8 μg/ml and to be susceptible to piperacillin-tazobactam (67% versus 15%; $P < 0.0001$). Although they were uncommon ($n = 11$), strains for which ceftriaxone MICs but not ceftazidime MICs were above 8 μg/ml were also more likely (55% versus 37%) to give ESBL-positive results. This was not true for strains ($n = 23$) for which ceftazidime but not ceftriaxone MICs were above 8 μg/ml (41% versus 59%).

Further analysis of β-lactam MICs was undertaken to determine whether there were optimum MICs that would aid in distinguishing ESBL-positive strains (Table 3). A ceftazidime MIC of >2 μg/ml, a ceftriaxone MIC of >1 μg/ml, a cefepime MIC of >0.25 μg/ml, and an aztreonam MIC of >1 μg/ml all had excellent sensitivity but only moderate specificity. Thus, all would be reasonable choices as tests for selecting those strains on which synergy testing should be performed. Only cefepime at >0.25 μg/ml gave significantly better specificity (74%) than the conventional broad-spectrum cephalosporins or aztreonam (67 to 69%), although its specificity was low (26%) among the subset of strains that were non-ceftazidime-ceftriaxone susceptible.

We also examined the antibiograms to determine whether other resistances or combinations of resistances could be used to predict which strains were ESBL positive. In strains selected for ceftazidime and/or ceftriaxone nonsusceptibility, piperacillin-tazobactam susceptibility (MIC ≤ 16 μg/ml) and nonsusceptibility to nalidixic acid (MIC > 8 μg/ml), gentamicin (MIC > 4 μg/ml), tetracycline (MIC > 8 μg/ml), and trimethoprim-sulfamethoxazole (MIC > 1 μg/ml) were moderately predictive of the presence of ESBLs (Table 3).

Although there are no NCCLS methods for detecting ESBLs in *Enterobacter* species, we believe that the methods used here provide consistent and valid results. The emergence of ESBLs in *Enterobacter* species has been unexpected, given the high propensity of this genus to generate mutants stably derepressed for group 1 cephalosporinase production. The competitive advantage of acquiring ESBLs to *E. cloacae* is unclear, although potentially it could allow the species to acquire resistance to cefepime and similar cephalosporins by combining the ESBL (to which they are vulnerable) with stably derepressed AmpC enzyme (to which they are not). It has been suggested that the acquisition of ESBLs may be related to the acquisition of plasmids encoding other resistances such as aminoglycosides (27). The very frequent (69% of ESBL-positive strains) association with gentamicin resistance in our study supports this view. Judging on the basis of our findings, the same may also be true for resistance to tetracycline and trimethoprim-sulfamethoxazole.

We were surprised to find as many as 16% of strains showing ESBL production in *E. cloacae* in a range of countries from our region. ESBL producers were found in all countries, although there was a wide range (3 to 44%) of prevalence. As expected, ESBL-producing strains were often resistant to a range of other compounds, including gentamicin, tobramycin, ciprofloxacin and other fluoroquinolones, tetracycline, and trimethoprim-sulfamethoxazole. Multiresistance was more fre-

quent than for ESBL-negative and broad-spectrum cephalosporin-susceptible strains. These findings are consistent with the suggestion that their presence reflects coselection by other antimicrobial classes.

Detection and recognition of ESBL-producing *Enterobacter* species has been a diagnostic problem. It has been generally assumed that resistance to broad-spectrum cephalosporins implies that a strain has stable derepression of *ampC*. With the emergence of ESBLs in *Enterobacter* spp. and the demonstration that some of these strains can disseminate widely (3), reliable methods of screening and detection of ESBL-producing *Enterobacter* spp. and other non-*E. coli*–non-*K. pneumoniae Enterobacteriaceae* are needed. The screening methods (i.e., using ceftazidime or cefotaxime or ceftriaxone or aztreonam with MICs of $\geq$2 μg/ml for the strains) recommended for *E. coli* and *K. pneumoniae* (21) may not be adequate for *Enterobacter* spp. due to the presence of constitutively chromosomally inducible AmpC β-lactamase. However, the results of our study showed that an increased (>0.25 μg/ml) cefepime MIC may represent a reliable marker for the presence of an ESBL. In addition, Tzelepi and coworkers have shown that double-disk synergy testing using 20-mm spacing works reasonably well with cefepime (and, to a lesser extent, cefpirome and aztreonam) as a substrate (29). The use of ceftazidime, cefotaxime, and ceftriaxone at 20-mm spacing detected less than half of the ESBL-producing *Enterobacter* spp. Thus, synergy testing with cefepime may be most reliable in detecting the ESBL phenotype in this genus and possibly others with the AmpC enzyme.

Enterobacter species harboring ESBLs have now been described for several countries worldwide (1–2, 6–11, 13, 15–17, 19, 23, 25–26, 28–30). Initially, the ESBLs in *Enterobacter* species were typical TEM or SHV enzymes (8–11, 16, 19, 23–26), but enzymes of the CTX-M class have been described more recently (1–4, 6, 7, 12). ESBLs of the VEB-1 type have been found in *Enterobacter* spp. from Thailand (13), the IBC-1 type in Greece (17), and the SFO type in Japan (20). We have detected ESBL-producing strains of *E. cloacae* in all eight countries and locales in our region, suggesting that ESBL enzymes are much more widely distributed than has previously been considered. Molecular studies, including isoelectric focusing, PCR, and ribotyping studies, are in progress to determine the predominant types and to provide any evidence of clonality. In particular, analysis for detection of the presence of CTX-M genes would be of interest, as there is only scant information on sensitivity to ceftriaxone, the broad-spectrum cephalosporin that we used in our studies, as a consequence of the effects of these enzymes (31).

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